Remarks/Arguments

The present amendment without prejudice to future prosecution: amends claims 1-5, 19, and 20; cancels claims 8-18; adds new claims 21-32; and amends the specification. Cancelled claims 8-18 were withdrawn from consideration by the examiner for being directed to a non-elected invention.

Claim 1 was amended to indicate up to 15 amino acid alterations from SEQ ID NO: 1, and provide editorial revisions to reference "A polypeptide immunogen" and "said polypeptide immunogen". Support for referencing up to 15 amino acid alterations from SEQ ID NO: 1 is provided in the specification, for example, on page 7, second full paragraph.

Claim 2 was amended to indicate up to 10 amino acid alterations from SEQ ID NO: 1, and provide an editorial revision to reference "polypeptide immunogen". Support for referencing up to 10 amino acid alterations from SEQ ID NO: 1 is provided in the specification, for example, on page 7, second full paragraph.

Claims 3, 4, 19 and 20 were amended to provide an editorial revision to reference "polypeptide immunogen".

Claim 5 was amended to indicate up to 15 amino acid alterations from SEQ ID NO: 1, to provide an editorial revision to reference "the amino terminus", and to remove reference to "said additional region or moiety is different from a sai-1 region."

New claims 21-25 depend from claim 19 and further describe the polypeptide immunogen. Support for the new claims is provided in the application, for example, on page 7, second full paragraph.

New claim 26 is directed to a composition comprising an immunologically effective amount of a polypeptide immunogen consisting of an amino acid sequence with up to 15 amino acid alterations from SEQ ID NO: 1 and a pharmaceutically acceptable carrier, wherein the polypeptide immunogen provides protective immunity against a *S. aureus* comprising a polypeptide of SEQ ID NO: 7. The description concerning the ability to provide protective immunity against *S. aureus* comprising a polypeptide of SEQ ID NO: 7 refers to a property of the polypeptide and is not a method limitation as to the actual use of the polypeptide.

SEQ ID NO: 7 provides the *S. aureus* COL sai-1 sequence. (The present application at page 4, last paragraph.) Support for the ability of a SEQ ID NO: 1 related polypeptide to provide

protective immunity against *S. aureus* comprising a polypeptide of SEQ ID NO: 7 is provided in the application, for example, by: (1) the ability of the SEQ ID NO: 1 related polypeptide, SEQ ID NO: 3, to provide protective immunity (see Example 1 of the present application at pages 15-18); and (2) SEQ ID NO: 1 corresponding to a fragment of SEQ ID NO: 7, where SEQ ID NO: 1 also has an added methionine (see, for example, the application at page 6, first paragraph and Figures 1 and 3). Figure 1 provides SEQ ID NO: 1. Figure 3 provides a comparison that includes SEQ ID NO: 7 and SEQ ID NO: 3. SEQ ID NO: 3 differs from SEQ ID NO: 1 by the presence of a His-tag.

New claims 27-32 further describe the polypeptide present in claim 26. Support for new claims 27-32 is provided, for example, on page 8, the fifth and sixth paragraph (referencing substantially purified) and on page 7, second full paragraph.

The specification was amended to provide a sequence identifier for LPXTG, to provide a sequence listing referencing LPXTG and to capitalize trademarks. The enclosed Sequence Listing has an updated general information section. No new matter is introduced into the Sequence Listing. The contents of the enclosed paper and computer readable form of the Sequence Listing are the same.

Objections to the Specification

The specification was objected to for failing to provide a sequence identifier for LPXTG, not providing LPXTG in the sequence listing, and failing to capitalize trademarks. The specification was amended to address these objections.

35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1-7, 19 and 20 stand rejected as allegedly lacking written description support. The rejection argues the specification fails to disclose a correlation between the function and the precise structure or epitope(s) responsible for providing protective immunity. The function upon which the rejection is based is the capacity to provide protective immunity against homologous or heterologous strains or serotypes of S. aureus. The rejection refers to Cruse et al., (Illustrated Dictionary of Immunology, 2nd Edn., CRC Press, 2003), Coleman (Research Immunol. 145:33-36, 1994), McGuinness et al., (Mol. Microbiol. 7:505-514, Feb 1993), and McGuinness et al.,

(Lancet 337:514-517 March 1991) as references pointing out the differences between linear and conformational epitopes and providing examples of where a single amino acid alteration can change the immunogenic properties of a polypeptide. The rejection is respectfully traversed.

The specification reasonable conveys to those skilled in the art that that applicants were in possession of polypeptides having a substantially similar sequence to SEQ ID NO: 1 that are able to provide protective immunity against *S. aureus*. The claims provide for a very high degree of sequence identity to SEQ ID NO: 1.

To meet the written description requirement "applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention." In re Alton,* 37 USPQ2d 1578, 1581, 76 F.3d 1168, 1172 (Fed. Cir. 1996), quoting Vas-Cath Inc. v. Mahurkar 935 F.2d 1563-1564, 19 USPQ 1111, 1117 (Fed. Cir. 1991). The written description requirement can be satisfied by:

> Show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* **or some combination of such characteristics**. [Bold emphasis added.]

Enzo Biochem, Inc. v. Gen-Probe Inc., 63 USPQ2d 1609, 1613, 323 F.3d 956, 964 (Fed. Cir. 2002), citing to and discussing Patent Office Written Description Guidelines provided in 66 Fed. Reg. 1099, 1106 (January 5, 2001).

Importance of Indicated Structural Relationship

The rejection fails to provide adequate support for the argument that one skilled in the art would not expect polypeptides in general having up to 15 amino acid alterations from SEQ ID NO: 1 would provide protective immunity against *S. aureus*. Instead, the rejection is based on the possibility that some unidentified alterations to SEQ ID NO: 1 could result in a polypeptide lacking protective immunity.

The skilled artisan reviewing the specification would expect sequences having up to 15 amino acid alterations from SEQ ID NO: 1 to provide protective immunity. The expectation is based on the high probability that altering up to 15 of the amino acids within the 260 amino acids

provided in SEQ ID NO: 1 will result in a polypeptide retaining the ability to provide protective immunity against *S. aureus*.

There are relatively a small number of amino acids required to provide an epitope, and for conformational epitopes, a relatively small number of amino acids are essential for maintaining the overall polypeptide confirmation. For example, McGuinness et al. in Table 1 lists several different epitopes, where the overall average epitopes is only about 6 amino acids. (McGuinness et al., Mol. Microbiol. at page 508.) Assuming an epitope size of 6 amino acids makes it unlikely that altering 15 of 260 amino acids will effect any particular epitope.

The expectation that a particular sequence based on SEQ ID NO: 1 would provide protective immunity increases as the relationship to SEQ ID NO: 1 increases. However, the rejection appears to be directed against any number of alterations that could be made, without taking into account the likelihood that any particular alteration made in SEQ ID NO: 1 will not be made to a epitope region or a region involved in conformation of the epitope, such that the polypeptide will no longer be protective.

Different Strains of *S. aureus*

The rejection is also based on the argument that it is not known how widely prevalent the targeted polypeptide (sal-1) is in different strains of *S. aureus* and if the targeted protein is serotype-specific, *spa* serotype-specific, or phage-type specific the antigenic determinants would have variant structures. It is respectfully submitted that the rejection: (1) fails to provide evidence that the targeted polypeptide is serotype-specific, *spa* serotype-specific, or phage-type specific such that the polypeptide would not be expected work to generally work in different strains; and (2) improperly requires a particular polypeptide to provide protection against all strains of *S. aureus*.

The targeted sai-1 polypeptide is referred to as StbA in Taylor et al., (Molecular Microbiology (2002) 43(6), 1603-1614). (See the present application at page 6, second paragraph.) Taylor al., while failing to indicate that StbA can be successfully targeted to produce a protective immune response, does indicate that StbA is a transferrin binding protein and based upon different *S. aureus* sequences, that the *stbA* coding region is well conserved among different *S. aureus* stains. (Taylor et al. at page 1607, first column, last paragraph.)

Polypeptides having a high degree of sequence identity to SEQ ID NO: 1 would be expected to produce a similar immune response as SEQ ID NO: 1 and be effective against strains of *S. aureus* expressing a closely related sequence.

With respect to a particular polypeptide immunogen, it is not necessary that the polypeptide provide protective immunity against every possible strain of *S. aureus* to fulfill the written description requirement. All that is needed is for polypeptide to be expected to provide protective immunity against at least one strain of *S. aureus,* such as *S. aureus* COL. For example, while it is expected that a particular polypeptide such as a polypeptide of SEQ ID NO: 1 would be useful against more than one strain, possession of a polypeptide of SEQ ID NO: 1 providing protective immunity does not require SEQ ID NO: 1 to provide protective immunity against every *S. aureus* strain.

35 U.S.C. § 112, Second Paragraph (Definiteness)

The examiner indicates that several claims are indefinite and provides suggestions for rendering the claims more definite.

Claim 1 was indicated to be indefinite based on reference to "said polypeptide" and "an polypeptide". Claim 1 was amended as suggested by the examiner to reference "said polypeptide immunogen" and "A polypeptide".

Claims 2-4, 19 and 20 were indicated to be indefinite based on reference to "The polypeptide of claim . . . ". Claims 2-4, 19 and 20 were amended as suggested by the examiner to refer to "The polypeptide immunogen of claim . . ."

Claim 5 was indicated to be indefinite based on reference to a "region or moiety different from a sai-1 region". Claim 5 was amended to delete the objected to phrase.

Claim 5 was also indicated to be indefinite based on reference to "amino terminus". Claim 5 was amended as suggested by the examiner to indicate "the amino terminus".

35 U.S.C. § 102 (Foster et al. ADA89581)

Claim 1, 2, 4 and 19 stand rejected as allegedly anticipated by Foster et al. (WO 2003011899) ('899). The rejection references Foster et al. ADA89581 and provides a sequence comparison between a SEQ ID NO: 1 region and a region from ADA89581. The rejection is respectfully traversed.

As noted above, claim 1 was amended from up to 26 to up to 15 amino acid alterations. Claim 1 references "consisting of an amino acid sequence with up to 15 amino acid alterations from SEQ ID NO: 1". As discussed below, because of the number of amino acid alterations between SEQ ID NO: 1 and ADA89581 the amendment does not impact the present anticipation rejection.

ADA89581 has over 100 amino acid alterations from SEQ ID NO: 1. Attached is a sequence alignment of full-length SEQ ID NO: 1 and ADA89581 (SEQUENCE ALIGNMENT 1). At the amino terminus ADA89581 has over 50 amino acids not provided for in SEQ ID NO: 1, and at the carboxyl terminus SEQ ID NO: 1 has over 50 amino acids not provided for in SEQ ADA89581.

35 U.S.C. § 102 (Foster et al. AAU75475)

Claim 1, 2, 4 and 19 stand rejected as allegedly anticipated by Foster et al. (WO 200198499) ('499). The rejection references Foster et al. AAU75475 and provides a sequence comparison between a SEQ ID NO: 1 region and a region from AAU75475. The rejection is respectfully traversed.

As noted above, Claim 1 was amended from up to 26 to up to 15 amino acid alterations. Claim 1 references "consisting of an amino acid sequence with up to 15 amino acid alterations from SEQ ID NO: 1". As discussed below, because of the number of amino acid alterations between SEQ ID NO: 1 and AAU75475 the amendment does not impact the present anticipation rejection.

AAU75475 has over 250 amino acid alterations from SEQ ID NO: 1. Attached is a sequence alignment of full-length SEQ ID NO: 1 and AAU75475 (SEQUENCE ALIGNMENT 2). At the amino terminus AAU75475 has over 220 amino acids not provided for in SEQ ID

NO: 1, and at the carboxyl terminus SEQ ID NO: 1 has over 30 amino acids not provided for in AAU75475.

35 U.S.C. § 102 (Foster et al. ADA89548)

Claim 1-3, 19 and 20 stand rejected as allegedly anticipated by Foster et al. '899. The rejection references Foster et al. '899 ADA89548 and provides a sequence comparison between a region from SEQ ID NO: 1 and a region from ADA89548. The rejection also indicates that ADA89548 elicits opsonic (i.e. protective) antibodies. The rejection is respectfully traversed.

As noted above, the Claim 1 was amended from up to 26 to up to 15 amino acid alterations. Claim 1 references "consisting of an amino acid sequence with up to 15 amino acid alterations from SEQ ID NO: 1". As discussed below, because of the number of amino acid alterations between SEQ ID NO: 1 and ADA89548 the amendment does not impact the present anticipation rejection.

ADA89548 has over 80 amino acid alterations from SEQ ID NO: 1. Attached is a sequence alignment of full-length SEQ ID NO: 1 and ADA89548 (SEQUENCE ALIGNMENT 3). At the amino terminus ADA89548 has two substitutions and over 50 additional amino acids not provided for in SEQ ID NO: 1, and at the carboxyl terminus SEQ ID NO: 1 has over 30 amino acids not provided for in ADA89548.

With respect to the examiners comments concerning the ability of ADA89548 to elicit opsonic antibodies, the rejection fails to indicate where Foster et al. '899 provides the skilled artisan with a reasonable expectation of success that ADA89548 provides protective immunity. For example, Foster et al. '899 does not appear to provide any data concerning the ability of ADA89548 or a polypeptide with a very high sequence identity to ADA89548 to provide protective antibodies.

35 U.S.C. § 103

Claims 5-7 stand rejected as allegedly obvious based on Foster et al. ('899) or Foster et al. ('499), in view of Devi et al. (US 6855807). Devi et al. is cited for adding additional sequence tags to a polypeptide to facilitate purification. The rejection is respectfully traversed.

As noted above, claim 5 was amended from up to 26 to up to 15 amino acid alterations. The difference between up to 15 and up to 26 amino acids does not impact the present rejection. As discussed above in the response to 35 U.S.C. § 102 rejections the Foster et al. polypeptides referenced by the rejection contain far more than 26 alterations from SEQ ID NO: 1.

Devi et al. does not cure the deficiency in Forster et al. with respect to the differences between the polypeptides described in Forster et al. references and the polypeptides provided in the claims. Devi et al. is cited for adding an additional sequence tag region.

Please charge deposit account 13-2755 for fees due in connection with this amendment. If any time extensions are needed for the timely filing of the present amendment, applicants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

By _____

Sheldon O. Heber
Reg. No. 38,179
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-1958